Remarks

Claims 1 to 16 were pending and before the Examiner. Claims 1 to 4 have been amended herein to improve the readability of the claims without changing the claim scope. Claims 1 to 16, as amended, are now pending and before the Examiner.

The Examiner rejected claims 2 to 4, 6 to 8, 10 to 12, and 14 to 16 under 35 U.S.C. § 112, second paragraph, as allegedly embracing hydrates outside the scope of claim 1 from which they all ultimately depend.

In response, without conceding the correctness of the Examiner's allegation, applicants have amended claim 1 and maintain that such amendment renders the Examiner's rejection moot. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner also rejected claims 9 to 16 under 35 U.S.C. § 112, second paragraph, as allegedly having indeterminate scope.

In response, applicants traverse the rejection and maintain there is nothing prohibited about defining the scope of treatable diseases by the mechanism of treatment (i.e, inhibition of the cellular Na^+/H^+ exchange) nor does it render the claims indefinite. The Examiner cites no authority for such a conclusion. Nor is it required under the existing caselaw or practice of the Office that applicants establish some level of "success rate" if the compounds have been shown to have a biological activity that reasonably correlates with a therapeutic use. The Examiner cites no authority for such a conclusion. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner also rejected claims 9 to 16 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled.

In response, applicants traverse the rejection and maintain the claims are enabled for treating diseases in which inhibition of the cellular Na^+/H^+ exchange is of therapeutic benefit. It is undisputed that the compounds of the claimed invention have a biological activity that reasonably correlates with a therapeutic use. Thus, in contrast with *In re Ruskin*, 148

U.S.P.Q. 221 (C.C.P.A. 1966) cited by the Examiner, where the application was "devoid of quantitative data" that supported the speculative utility of that invention which had little or no apparent established analogy in the art, the instant claims are directed to a novel benzoylguanidine derivative having advantageous properties (see page 4, lines 11 to 12) that is related to prior art benzoylguanidine compounds that have established therapeutic uses and supports the use claimed herein (see page 1, line 13, to page 2, line 24). Furthermore, *Ex parte Jovanovics*, 211 U.S.P.Q. 907 (P.T.O. Bd. App. 1980) also cited by the Examiner but involving only a 35 U.S.C. § 101 (utility) rejection, reversed the rejection as to the N-formyl derivatives claimed (which had evidence supporting its utility) and only upheld the rejection as to the N-desmethyl derivatives, which even the applicants conceded the was no data demonstrating their effectiveness. Such is obviously not the case here and neither *In re Ruskin* nor *Ex parte Jovanovics* is relevant. Applicants note that the Office has been repeatedly reversed in creating requirements for patentability that are properly within the province of the FDA. *See, e.g.*, M.P.E.P. § 2107 (particularly §§ 2107.01 III/IV and 2107.03) and § 2164 (particularly § 2164.06). It is not required that applicants provide *in vivo* test data about compounds that have been shown to have a useful biological activity. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner rejected claims 1, 5, 9, and 13 under 35 U.S.C. § 103(a), as allegedly unpatentable over Eickmeier *et al.* '207 (U.S. Patent No. 6,323,207) or Eickmeier *et al.* '176 (WO 00/17176) and Buerger *et al.* '335 (U.S. Patent No. 6,114,335) or Buerger *et al.* '253 (WO 97/262253). The Examiner also rejected claims 1, 5, 9, and 13 under the judicially created doctrine of double patenting over unspecified claims of Eickmeier *et al.* '207.

In response, applicants respectfully traverse the Examiner's obviousness rejection and double patenting rejection and contend that both rejections are improper. A *prima facie* case of obviousness requires the satisfaction of three criteria: (i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (ii) there must be a reasonable expectation of success; and (iii) the references when combined must teach or suggest all of the claim limitations. M.P.E.P. § 2143.

As pointed out in the specification (see page 2, line 22 to page 4, line 12, emphasis added):

The abovementioned pharmacologically valuable properties of the benzoylguanidine derivatives disclosed in the prior art are the main prerequisite for effective use of a compound as a pharmaceutical composition. An active substance, however, has to satisfy still more requirements in order to be allowed to be used as a medicament. These parameters are largely connected to the physico-chemical nature of the active substance.

Without being restricted thereto, examples of these parameters are the stability of effect of the starting substance under different ambient conditions, stability during the production of the pharmaceutical formulation, and stability in the finished compositions of the medicament. The pharmaceutical active substance used to prepare the pharmaceutical compositions should therefore have high stability which must also be guaranteed even under different ambient conditions. This is absolutely necessary to prevent the use of pharmaceutical compositions which contain breakdown products of the active substance, for example, in addition to the active substance itself. In such a case, the content of active substance present in pharmaceutical formulations may be lower than specified.

The absorption of moisture reduces the content of pharmaceutical active substance because of the increase in weight due to the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, for example, by the addition of suitable drying agents or by storing the pharmaceutical composition in an environment which is protected from damp. Moreover, the uptake of moisture may reduce the content of pharmaceutical active substance during manufacture if the pharmaceutical composition is exposed to the environment without any protection from moisture whatsoever. Preferably, therefore, a pharmaceutical active substance should be only slightly hygroscopic.

As the crystal modification of an active substance can influence the activity of a pharmaceutical composition, it is necessary to clarify any existing polymorphism of an active substance present in crystalline form as much as possible. If there are different polymorphic modifications of an active substance, care must be taken to ensure that the crystalline modification of the substance does not change in the subsequent pharmaceutical preparation. Otherwise, this could have a detrimental effect on the reproducible activity of the medicament. In this context, active substances which are characterized by limited polymorphism are preferred.

Another criterion which may be of exceptional importance in certain circumstances, depending on the choice of formulation or on the choice of the method of production of the formulation, is the solubility of the active substance. If, for example, pharmaceutical solutions are prepared (for example for infusions), it is essential that the active substance is sufficiently soluble in physiologically acceptable solvents. A sufficiently soluble active substance is also very important for pharmaceutical compositions administered orally.

The underlying aim of the present invention is to prepare a pharmaceutical active substance which is not only characterized by a potent pharmacological activity but also satisfies as far as possible the physico-chemical requirements referred to above.

* * *

The compound of formula **1** is not hygroscopic and dissolves readily in physiologically acceptable solvents. It is also characterized by a high degree of stability.

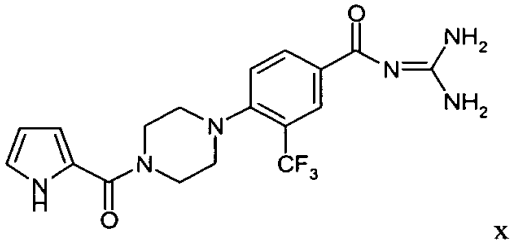
These advantageous properties is in contrast to the compounds of Eickmeier *et al.* '207, Eickmeier *et al.* '176, Buerger *et al.* '335, and Buerger *et al.* '253, which neither suggest or provide motivation to make the compounds of the instant claimed invention nor provide a reasonable expectation of success, let alone disclose or suggest these surprising advantages over the cited prior art. Furthermore, the Examiner has not specified what claims of Eickmeier *et al.* '207 are deemed relevant to the double patenting rejection. As this is a required element of the double patenting analysis, applicants respectfully request that the Examiner specify what claims of Eickmeier *et al.* '207 are at issue. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections.

Applicants maintain that the remarks above render the Examiner's rejections moot as to all the pending claims. Applicants therefore submit that all the pending claims are allowable and respectfully solicit a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Version of the Claims with Markings to Show Changes Made by this Amendment

In accordance with 37 C.F.R. § 1.121(c)(1)(ii), the following marked up version of the claims amended herein is provided to show all of the changes relative to the previous version of the claims before the amendments herein.

--1. (Amended) 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethylbenzoylguanidine hydrochloride **1**



x HCl **1,**

or a hydrate thereof.--

--2. (Amended) The compound according to claim 1, wherein the compound is ~~present in the form of one of its~~a hydrates.--

--3. (Amended) The compound according to claim 1, wherein the compound is ~~present in the form of its~~a monohydrate.--

--4. (Amended) The compound according to claim 1, wherein the compound is ~~present in the form of its~~a hemihydrate.--

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on June 16, 2003.

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6-16-2003
Dated

Respectfully submitted,

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